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Relationship among Parkinson's disease, constipation, microbes, and microbiological therapy

Yuan XY *et al*. Microbes and PD-related constipation

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Abstract

This comprehensive review elucidates the complex interplay between gut microbiota and constipation in Parkinson's disease (PD), a prevalent non-motor symptom contributing significantly to patients' morbidity. A marked alteration in the gut microbiota, predominantly an increase in the abundance of *Proteobacteria* and *Bacteroidetes*, is observed in PD-related constipation. Conventional treatments, although safe, have failed to effectively alleviate symptoms, thereby necessitating the development of novel therapeutic strategies. Microbiological interventions such as prebiotics, probiotics, and fecal microbiota transplantation (FMT) hold therapeutic potential. While prebiotics improve bowel movements, probiotics are effective in enhancing stool consistency and alleviating abdominal discomfort. FMT shows potential for significantly alleviating constipation symptoms by restoring gut microbiota balance in patients with PD. Despite promising developments, the causal relationship between changes in gut microbiota and PD-related constipation remains elusive, highlighting the need for further research in this expanding field.

Key Words: Parkinson disease; Constipation; gut microbiota; Prebiotics; Probiotics; Fecal microbiota transplantation

Core Tip: This comprehensive review explores the intricate relationship between gut microbiota and constipation, a prevalent non-motor symptom observed in Parkinson's disease (PD). Notably, we discuss the significant alterations in gut microbiota, particularly the increase in the abundance of *Proteobacteria* and *Bacteroidetes*, associated with PD-related constipation. Although currently available treatments are safe, their effectiveness in providing symptom relief remains suboptimal, necessitating the development of innovative therapeutic approaches. This review delves into the potential of therapies based on microbiological interventions such as prebiotics, probiotics, and fecal microbiota transplantation, in alleviating these symptoms.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder with an increasing incidence worldwide[1]. The doubling of PD cases between 1990 and 2016 is expected to result in more than 12 million patients globally by the year 2050[2,3]. PD is characterized by both motor symptoms (*e.g.*, bradykinesia, resting tremor, and rigidity) and non-motor symptoms (*e.g.*, constipation, depression, impaired olfaction, and rapid eye movement sleep behavior disorder)[4]. Constipation is considered one of the most common precursor symptoms of PD and persists throughout the clinical stages of the disease, with its prevalence increasing as the disease progresses[5,6]. For patients with PD, constipation significantly reduces their ability to carry out daily activities and their overall quality of life[7]. Hence, effective therapeutic approaches to control PD-related constipation are urgently required. The pathological mechanisms of PD-related constipation remain unknown, but they may be associated with recto-anal dysfunction or smooth muscle dystonia in the gastrointestinal tract[8,9]. The role of intestinal microorganisms has attracted increasing research attention in recent years. Accumulating evidence reveals a relationship between gut microbiota and PD-related constipation[10–12]. Consequently, traditional treatment options are shifting toward microecological interventions[13–16]. This review summarizes currently available evidence supporting the roles of gut microbiota

in the pathogenesis and treatment of PD-related constipation.

MICROBIOTA-GUT-BRAIN AXIS

The role of intestinal microbes in the central nervous system (CNS) has garnered increasing interest recently. The gut microbiota is a complex ecological community comprising hundreds of millions of microbes that live in the gut and regulates both normal physiology and disease susceptibility through its collective metabolic activities and host interactions[17]. A growing body of research linking PD to the microbiota-gut-brain axis suggests that gut microbiota and microbial metabolites have an important role in PD pathogenesis by influencing neuroinflammation, barrier function, and neurotransmitter activity[18,19]. The microbiota-gut-brain axis includes the autonomic nervous system, the enteric nervous system (ENS), the hypothalamic-pituitary-adrenal axis, and the intestinal microbes[18]. The gut microbiota and the brain can communicate directly through various signaling molecules or indirectly through the gut-brain axis; similarly, the brain can influence the microbes directly or indirectly through alterations to the gut microbiota environment[20].

BRAAK'S HYPOTHESIS

The pathological hallmarks of PD are loss of dopaminergic neurons together with abnormal accumulation of α-synuclein (α-syn) in the substantia nigra and the striatum[21]. Braak *et al*[22] and Hawkes *et al*[23] noticed α-synuclein-containing inclusion bodies in the intestines of patients with sporadic PD and hypothesized that the pathology of Lewy body in PD might begin in the gastrointestinal tract and then spread to the brain through the vagal nerve. Human α-syn fibrils were injected into the gut tissue of healthy rodents and transported through the vagus nerve to the dorsal motor nucleus of the vagal nucleus in the brainstem. These results provide the first direct experimental proof that α-syn can propagate from the gut to the brain[24]. Vagotomy has protective effects on the subsequent development of PD, as it can attenuate the pathological spread of α-syn, dopaminergic neuronal degeneration, and motor dysfunction. The vagus nerve is an important route

for the transmission of pathological α-syn into the CNS[25–28]. These findings demonstrate that a-syn detection in the ENS could provide an opportunity to identify early PD neuropathology before the disease spreads to other regions and motor symptoms become evident. Shannon *et al*[29] reported a-syn detection in the neurites of the colonic submucosa in colonic biopsies collected 2-5 years before motor symptom onset in patients with PD[29]. This evidence suggests that a-syn detection in colonic mucosal biopsy samples could serve as a presymptomatic biomarker for PD. Additional evidence revealing a-syn accumulation in colonic biopsies for up to 8 years before motor symptom manifestation further supports the potential of enteric a-syn as a diagnostic biomarker for PD[30]. Pouclet *et al*[31] performed a comparative analysis of a-syn deposition using biopsy samples collected from the rectum, descending colon, and ascending colon of 26 patients with PD and 9 control subjects. The authors discovered that 23%, 42%, and 65% of patients with PD had a-syn deposition in the rectum, descending colon, and ascending colon, respectively, while control subjects had no a-syn deposition. These findings indicate that enteric α-syn detection has the potential to be used as a sensitive, PD-specific, and clinically useful biomarker for early PD detection.

CONSTIPATION IN PD

Constipation, a prevalent non-motor symptom of PD, has been observed in as many as 90% of patients and is a notable early manifestation and risk factor for PD[32–34]. It is nearly three times more prevalent in patients with PD than in healthy individuals[8,35]. Research indicates that the severity of PD-related constipation helps diagnose the PD stage, with 67% sensitivity and 90% specificity[36]. A Taiwanese study revealed that constipation severity correlates with the probability of PD development[37]. A meta-analysis supported this finding, indicating a 2.27-times higher risk of PD in individuals with constipation[33]. Constipation has a significant 76.56% effect on PD and is mediated by gut microbial changes, as a result of altered gut conditions caused by constipation[12,38]. These changes may result in intestinal inflammation and PD symptoms[38]. Causes of PD-related constipation include delayed colon transit and outlet obstruction[8,39]. The clinical course

of PD worsens with constipation, resulting in evident severe motor and non-motor symptoms[7,40]. The severity and frequency of constipation also increase as PD advances[41,42]. A unique correlation between gut health and cognitive function has been documented in patients with PD[43]. Studies from Spain suggest a link between constipation and cognitive decline in PD[44]. The presence and severity of constipation are associated with rapidly progressive dementia and reduced subcutaneous fat [45,46].

Evidence suggests an association between gastrointestinal dysfunction and PD medication[47]. Compared to patients with PD who have a normal colonic transit, those with a slow colonic transit require a considerably higher levodopa equivalent daily dose[48]. This indicates that slow colonic transit may delay peak plasma concentration and cause a reduction in the clinical efficacy of levodopa. Long-term PD-related constipation can lead to an abnormal overgrowth of bacterial decarboxylases in the gut[49]. Du *et al*[11] reported a significant increase in the abundance of the order *Lactobacillales* in the intestines of patients with PD-related constipation. Levodopa plasma availability has a negative association with *Lactobacillus* abundance[50], particularly as several bacterial species of the genus *Lactobacillus* contain genes encoding tyrosine decarboxylase[51]. This enzyme can convert levodopa, a common drug used for PD treatment, into dopamine, affecting blood dopamine levels and potentially causing motor fluctuations. This may necessitate more frequent administration of levodopa and decarboxylase inhibitor treatments[51]. Complex interactions occur between anti-PD medications and gastrointestinal symptoms[52]. Healthy rats treated with PD medication for 14 days exhibited significantly reduced gut motility and altered microbiota composition, including increased abundance of *Bifidobacterium* and *Lactobacillus* and decreased abundance of the families *Prevotellaceae* and *Lachnospiraceae*[50]. Alterations in microbiota composition may lead to microbial metabolite changes, leading to constipation. A comprehensive meta-analysis demonstrated that pramipexole administration increased constipation risk relative to placebo[53]. Evidence suggests that constipation marginally increased after 1 year in patients with PD on dopaminergic medication, particularly levodopa[54]. Another randomized, double-blind trial showed that pramipexole extended

release led to a higher constipation likelihood versus placebo in patients with early PD[55]. A high levodopa equivalent dose increases constipation risk, which nearly doubles with the combination of levodopa and a dopamine agonist[56].

Slow Colon Transit

Approximately 80% of patients with PD exhibit a slow colon transit, often twice as long as that recorded in healthy control subjects[39,57,58]. This delayed motility is a sign of impaired peristalsis, which depends on the ENS, a network of two plexuses (myenteric and submucosal) within the gut walls[59]. A significant number of these plexus neurons express vasoactive intestinal peptide (VIP) and nitric oxide synthase — both being crucial for muscle relaxation and vasodilation[60]. PD-associated Lewy bodies are present in VIPergic neurons of the ENS, implying that a slower intestinal transit could primarily result from impaired reflex relaxation caused by the loss of inhibitory motor neurons[61]. Evidence indicates Lewy body–containing neurons in the sympathetic ganglia are immunoreactive to tyrosine hydroxylase, implying that the slow transit could be directly linked to the involvement of colonic myenteric plexus in the PD course[62]. Additionally, the loss of dopaminergic neurons in the ENS likely contributes to slow-transit constipation. Studies have found that dopamine inhibits the release of acetylcholine and slows intestinal motility through presynaptic D2 receptors[63]. Age-related loss of excitatory cholinergic neurons in the colon may also be a factor for the slow colonic transit in PD[64,65]. The type of constipation influences the risk of PD development, and people with slow-transit constipation have a very high likelihood of developing PD[66]. Therefore, individuals aged over 65 years with newly diagnosed slow-transit constipation should be considered for PD screening[66].

Outlet Obstruction

More than 60% of patients with PD experience pelvic floor dyssynergia, an uncoordinated action of defecation muscles leading to outlet obstruction[67]. Normal defecation requires the relaxation of pelvic floor and sphincter muscles and a swift return

of muscle activity post-defecation. The increase in intra-abdominal pressure, aided by the contraction of glottic, diaphragmatic, and abdominal wall muscles, acts synergistically with the inhibition of pelvic floor and external anal sphincter muscles[68]. In patients with PD, constipation often correlates with a paradoxical contraction of the puborectalis muscle. This abnormal muscle behavior results in defecation obstruction, a decrease in the anorectal angle, and paradoxical perineum ascent[39,69]. PD-related constipation is indicative of significantly weaker gastrointestinal tract function, with slow transit suggesting colonic ENS involvement and outlet obstruction (dystonia) suggesting direct muscle involvement in PD[39]. The severity and duration of PD are closely associated with the degree of constipation[70].

GUT MICROBIOTA AND PD

In the context of gut microbiota and PD, functional gut changes in a PD mouse model appear well before the onset of motor symptoms, suggesting a potential gut origin for PD[71]. Alteration in gut function could influence PD progression by modifying gut microbiota composition[72]. Several studies have proposed that gut microbiota alteration could trigger PD development[73,74] and incite immunological activation[75]. Persistent immune responses in the gut can increase intestinal permeability, allowing microbial products and inflammatory mediators to escape from the gut, thereby stimulating systemic immune responses[76]. This proinflammatory immune activity and related conditions can elevate levels of α-synuclein (α-syn) in the gut[77]. Pathologic levels of α-syn can propagate in a prion-like manner from the gut to the brain through the vagus nerve[27,78,79]. One study suggested that oral administration of *Proteus mirabilis* stimulates α-synuclein aggregation in the brain and colon, resulting in PD symptoms[80]. Another research indicated that the abundance of specific bacterial families could identify patients with PD[36].

GUT MICROBIOTA AND PD-RELATED CONSTIPATION

Mechanism of Action between Gut Microbiota and PD-Related Constipation

Current evidence suggests a delayed colon transit and outlet obstruction, both linked to alpha-synuclein–related neurodegeneration in the ENS, are primary factors for PD-related constipation[36,81]. However, emerging research points out to the imbalance in gut flora as a significant player in the development and progression of PD-related constipation[82]. Studies have found that excessive pre-synaptic α-synuclein production in the colonic myenteric ganglia could cause early defecation impairment[83]. This finding is supported by the fact that transgenic mice overexpressing α-synuclein show impaired colonic transit[84,85]. Moreover, α-synuclein overexpression in the CNS can alter gut function[86,87]. Notably, transplantation of PD microbiota into humanized mice worsened motor symptoms and intestinal dysfunction, implying that α-synuclein overexpression and microbiota imbalance both contribute to disease progression[72]. Research also suggests that gut microbiota may significantly influence gut motor function[88,89]. This finding was confirmed in a study in which aryl hydrocarbon receptor expression induced by the gut microbiota in enteric neurons affected gut motility[90]. In a mouse model of PD induced by rotenone, gut microbiota was seen to influence gastrointestinal dysfunction, indicating its possible role in PD[91]. Distinct differences in gut microbiome between patients with PD and individuals without PD have been identified[92]. A study of 197 patients with PD demonstrated that higher microbial diversity in the gut correlated positively with stool firmness, implying a link between higher microbial diversity and constipation[93]. Furthermore, most PD studies have reported a decrease in the abundance of the families *Prevotellaceae* and *Lachnospiraceae*, accompanied by an increase in the abundance of the family *Verrucomicrobiaceae* (including the genus *Akkermansia*)[94–97]. This suggests a complex interplay between gut microbiota and PD-related constipation.

Studies reveal that gut microbiota dysbiosis may reduce stool water content, and *Prevotella* enterotypes increases the stool water content[98,99]. Indeed, patients with *Prevotella*-enriched enterotypes showed less severe constipation[100]. Hydrogen sulfide secreted by *Prevotella*, known for protecting dopaminergic neurons, may decrease in concentration in patients with PD who have reduced *Prevotella* enterotypes, leading to

constipation because of increased hydrogen sulfide absorption[101]. Hydrogen sulfide can inhibit colonic contractility by affecting cholinergic and tachykinergic excitatory pathways mediated by neurons[102]. *Prevotellaceae* and *Lachnospiraceae*, which produce short-chain fatty acids (SCFAs), can promote gastrointestinal peristalsis[103]. A correlation was found between the genus *Akkermansia*, particularly *Akkermansia muciniphila*, and colon transit time[104]. Uncontrolled growth of *Akkermansia muciniphila* may degrade the mucus layer, leading to drier or harder stools[105,106]. A study on 52 patients with PD found that Enterobacteriaceae, abundant in the colon of patients with PD, negatively correlated with stool frequency[107]. Enterobacteriaceae produce curli, an amyloid protein that can promote the aggregation of α-syn in the intestine and brain[80,108]. Gut-restricted amyloid inhibitor treatment in mice alleviated motor and constipation-like symptoms[108]. Both commensal and pathogenic bacterial metabolites can influence gut functions[93,109] (Figure 1). SCFAs, glucagon-like peptide 1 (GLP-1), and peptide tyrosine tyrosine (PYY) can modulate gut sympathetic activity and gastrointestinal motility, highlighting the link between gut microbiota and neuronal function[110]. Additionally, SCFAs activate G-protein-coupled receptors on enteroendocrine cells, mediating GLP-1 and PYY secretion[111]. *In vitro* studies showed that SCFAs stimulate colonic contractions through an enteric reflex involving local sensory and cholinergic nerves[112] and regulate colonic motility through enteric neurons[113]. Changes in the cholinergic phenotype caused by butyrate have a prokinetic effect on colonic motility[99,113]. Alterations in dopamine, 5-HT4 receptors, and β3-adrenoceptors likely lead to colonic dysmotility and constipation in patients with PD[114]. The β3-adrenoceptor in colonic interstitial cells of Cajal inhibits colonic motility by inhibiting pacemaker potentia[115]. Dopamine inhibits gastrointestinal motility by activating D1 receptors[116,117], while 5-HT promotes gut motility primarily through the 5-HT4 and 5-HT3 receptors[118,119]. SCFAs can activate 5-HT4 receptors of intrinsic sensory neurons, triggering a peristaltic colonic reflex[120]. Butyrate, which modulates gastrointestinal motility by stimulating 5-HT3 receptors of the vagal sensory fibers[121,122], negatively correlates with constipation severity[123] and increases mucin secretion[124]. Mucin acts as a lubricant, protecting the mucosa and aiding stool

excretion[125]. Acetic acid is positively associated with defecation frequency in patients with PD[126].

A study identified higher levels of the harmful amino acid metabolite p-cresol sulfate in the cerebrospinal fluid of patients with PD[127]. The protein degradation byproducts p-cresol and phenylacetylglutamine are also found elevated in the serum of patients with PD, with strong associations with stool consistency and constipation[93]. Glycerolipids, sphingolipids, and sterol lipids are positively associated with constipation in patients with PD[123]. Additionally, constipation positively correlated with pantothenic acid, D-ribose, L-lactic acid, D-alanine, and xanthine in the Luxembourg Parkinson's Study[128]. In summary, the altered microbiota composition in PD-related constipation might lead to changes in microbial metabolites, especially SCFAs, suggesting the potential for manipulating SCFAs as a novel therapeutic strategy in PD-related constipation. Correlations between PD-related constipation, microorganisms, and their metabolites are summarized in Table 1.

Gut Microbiota in PD-Related Constipation

Research indicates that the primary microorganisms in patients with PD-related constipation are those belonging to Proteobacteria and Bacteroidetes[14]. According to a study, the most prevalent bacteria in the fecal microbiota of patients with PD-related constipation were from the phylum *Bacteroidetes*, genus *Bacteroides*, order *Bacteroidales*, class *Bacteroidia*, and family *Bacteroidaceae*. The study also noted a significantly higher abundance of *Bacteroides* and a considerably lower abundance of *Faecalibacterium* in patients with PD-related constipation than in healthy controls[129]. Additionally, Du *et al*[11] reported that *Bifidobacteriales*, *Lactobacillales*, *Bacillales*, *Peptostreptococcales Tissierellales*, *Desulfovibrionales*, and *Coriobacteriales* were the most abundant microorganisms in the gut of patients with PD-related constipation. These patients also exhibited significantly higher levels of *Bacillus*, *Alistipes*, *Bifidobacterium*, *Romboutsia*, *Adlercreutzia*, *Desulfovibrio*, *Butyricicoccus*, *Bilophila*, *Intestinibacter*, *Holdemania*,*UCG_002* *Actinomyces*,

Lachnospiraceae_UCG_008, *Gordonibacter*, *Raoultibacter*, *Odoribacter*, *Oscillibacter*, *Eubacterium_nodatum*_group, and *uncultured* species than healthy individuals[11]. Interestingly, the gut microbiota of patients with chronic constipation is predominantly characterized by reduced abundance of *bifidobacteria* and *lactobacilli* and increased abundance of *Bacteroidetes*[130–133].

MICROBIAL TREATMENT FOR PD-RELATED CONSTIPATION

The current treatments for PD-related constipation mainly include prokinetics and laxatives. While these traditional therapies can be safe and effective, they are often limited in fully relieving clinical symptoms, indicating a need for more effective treatments[134,135]. Recent insights into the association between gut microflora and PD-related constipation have led to research exploring how altering gut microflora through prebiotics, probiotics, and fecal microbiota transplantation (FMT) might provide a cure. These interventions could supplement traditional treatments for PD-related constipation.

Prebiotics

Prebiotics are selectively utilized substrates that confer health benefits to host microorganisms[136]. Reports suggest that prebiotic fibers can alleviate constipation and improve bowel movements[137]. In particular, diets rich in insoluble fiber improved constipation in patients with PD[138], and a study reported that psyllium is useful in treating constipation in patients with PD, noting that it increased stool frequency and weight, with, on average, three bowel movements per week[139].

Probiotics

Probiotics are live microorganisms that confer health benefits to the host when administered in sufficient amounts and are thought to be another potential treatment for PD-related constipation. They can strengthen the gut barrier and restore normal intestinal microbiota[140], suggesting its potential as a novel treatment strategy for PD-related constipation[141,142]. Initial studies have shown promising results; for instance, patients

with PD who took Lactobacillus casei Shirota for 5 weeks showed improved stool consistency[16], and those who took probiotics containing *Lactobacillus acidophilus* and *Bifidobacterium infantis* for 3 months experienced reduced abdominal pain and bloating[10]. Further research showed an increase in the number of complete bowel movements in patients with PD-related constipation after drinking fermented milk containing multiple probiotic strains and prebiotic fiber for 4 weeks[143]. A subsequent study reported that taking a multi-strain probiotic combined with prebiotic fiber for 8 weeks improved whole-gut transit time and the frequency of bowel opening in patients with PD-related constipation[144]. Additionally, a randomized controlled trial of 72 patients with PD-related constipation showed that multi-strain probiotics significantly improved weekly spontaneous bowel movements frequency and quality of life scores associated with constipation[15]. Du *et al*[11] reported that multi-strain probiotics effectively improved constipation symptoms and stool consistency in patients with PD, even altering the composition of their gut microbiota.

Fecal Microbiota Transplantation

FMT is a novel treatment approach that alleviates constipation by restoring the intestinal microenvironment. This method is based on the premise that alterations in the microbiome may affect gut motility through the production of different microbial-derived metabolites, and correcting these disruptions might improve the clinical symptoms[145]. FMT has shown promising results in treating PD-related constipation, as evidenced by increased abundance of *Firmicutes* and decreased abundance of *Proteobacteria* and *Bacteroidetes* in treated patients, leading to effective relief of constipation and tremors[14]. More recent studies support the beneficial role of FMT in improving PD-related constipation symptoms[13]. One study highlighted that FMT significantly reduced Bacteroidetes and increased *Prevotella* and *Blautia* in patients with PD-related constipation. Surprisingly, after FMT, the abundance of several other bacterial groups also increased at different times, accompanied by significant decreases in the patients' Wexner constipation scores and resolution of their constipation symptoms[129].

Such findings underline the therapeutic potential of FMT in rebuilding the gut microbiota of patients with PD-related constipation. Microbial alterations in PD-Related constipation after microbial treatments are summarized in Table 2.

CONCLUSION

In prodromal PD, abnormalities related to α-syn can be detected in the colon. Subsequently, α-syn spreads from the gut to the brain through the vagus nerve, which may lead to the development of PD. Constipation is considered one of the precursor symptoms of PD, potentially stemming from α-syn pathology in the ENS. The exact mechanisms driving PD-related constipation are still largely unknown, with potential causes ranging from outlet obstruction to delayed colon transit. Current evidence shows a correlation between PD-related constipation and changes in gut microbiota, suggesting a complex interplay between the gut microbiome and PD-related constipation. However, whether the onset of PD-related constipation precedes intestinal dysbiosis or vice versa is still unknown. Despite the unclear cause-effect relationship, studies indicate that gut microbiota dysbiosis can exacerbate constipation and that restoring the gut microbiota can mitigate these symptoms, suggesting gut microbiota as a potential therapeutic target for PD-related constipation. Microbiological intervention treatments for PD-related constipation, including prebiotics, probiotics, and FMT, can prove beneficial and possibly more effective than traditional treatments.

This review covered longitudinal studies on gut dysbiosis in PD-related constipation. However, it has a few weaknesses. The limited number of studies may not have accurately captured the full longitudinal changes in the microbiota associated with PD-related constipation. Furthermore, there is a scarcity of clinical studies examining intestinal flora specifically in PD-related constipation, making it difficult to infer the particular microbial taxa linked to this condition. In addition, as most studies have been conducted at the phylum and genus levels, further research at the species and strain levels could provide greater mechanistic insights. Therefore, future studies should focus on identifying specific bacterial species that promote PD-related constipation

development. Finally, pinpointing the causative microbes could enable targeted microbial therapies for PD-related constipation in the future. However, more rigorous clinical studies are needed to elucidate the precise microbiota compositional and functional changes underlying PD-related constipation before such therapeutic approaches can be applied. However, this is a nascent field of research with various limitations and challenges and hence requires future extensive research.

REFERENCES

1 **Okunoye O**, Marston L, Walters K, Schrag A. Change in the incidence of Parkinson's disease in a large UK primary care database. *NPJ Parkinsons Dis* 2022; **8**: 23 [PMID: 35292689 DOI: 10.1038/s41531-022-00284-0]

2 **GBD 2016 Parkinson's Disease Collaborators**. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018; **17**: 939-953 [PMID: 30287051 DOI: 10.1016/S1474-4422(18)30295-3]

3 **Rocca WA**. The burden of Parkinson's disease: a worldwide perspective. *Lancet Neurol* 2018; **17**: 928-929 [PMID: 30287052 DOI: 10.1016/S1474-4422(18)30355-7]

4 **Kalia LV**, Lang AE. Parkinson's disease. *Lancet* 2015; **386**: 896-912 [PMID: 25904081 DOI: 10.1016/S0140-6736(14)61393-3]

5 **Safarpour D**, Sharzehi K, Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson's Disease. *Drugs* 2022; **82**: 169-197 [PMID: 35076890 DOI: 10.1007/s40265-021-01664-1]

6 **Schapira AHV**, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nat Rev Neurosci* 2017; **18**: 435-450 [PMID: 28592904 DOI: 10.1038/nrn.2017.62]

7 **Yu QJ**, Yu SY, Zuo LJ, Lian TH, Hu Y, Wang RD, Piao YS, Guo P, Liu L, Jin Z, Li LX, Chan P, Chen SD, Wang XM, Zhang W. Parkinson disease with constipation: clinical features and relevant factors. *Sci Rep* 2018; **8**: 567 [PMID: 29330419 DOI: 10.1038/s41598-017-16790-8]

8 **De Pablo-Fernández E**, Passananti V, Zárate-López N, Emmanuel A, Warner T. Colonic transit, high-resolution anorectal manometry and MRI defecography study of

constipation in Parkinson's disease. *Parkinsonism Relat Disord* 2019; **66**: 195-201 [PMID: 31473084 DOI: 10.1016/j.parkreldis.2019.08.016]

9 **Knudsen K**, Krogh K, Østergaard K, Borghammer P. Constipation in parkinson's disease: Subjective symptoms, objective markers, and new perspectives. *Mov Disord* 2017; **32**: 94-105 [PMID: 27873359 DOI: 10.1002/mds.26866]

10 **Georgescu D**, Ancusa OE, Georgescu LA, Ionita I, Reisz D. Nonmotor gastrointestinal disorders in older patients with Parkinson's disease: is there hope? *Clin Interv Aging* 2016; **11**: 1601-1608 [PMID: 27956826 DOI: 10.2147/CIA.S106284]

11 **Morris MJ**, Sartor O, de Bono JS, Fizazi K, Tagawa ST. Reply to Timothée Olivier, Kerrington Powell, Vinay Prasad. Lutetium-177-PSMA-617 in Metastatic Castration-resistant Prostate Cancer: Limitations of the VISION Trial. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2022.08.022. *Eur Urol* 2023; **84**: 7-8 [PMID: 37032186 DOI: 10.1016/j.parkreldis.2022.08.022]

12 **Fu SC**, Shih LC, Wu PH, Hsieh YC, Lee CH, Lin SH, Wang H. Exploring the Causal Effect of Constipation on Parkinson's Disease Through Mediation Analysis of Microbial Data. *Front Cell Infect Microbiol* 2022; **12**: 871710 [PMID: 35646722 DOI: 10.3389/fcimb.2022.871710]

13 **Segal A**, Zlotnik Y, Moyal-Atias K, Abuhasira R, Ifergane G. Fecal microbiota transplant as a potential treatment for Parkinson's disease - A case series. *Clin Neurol Neurosurg* 2021; **207**: 106791 [PMID: 34237681 DOI: 10.1016/j.clineuro.2021.106791]

14 **Huang H**, Xu H, Luo Q, He J, Li M, Chen H, Tang W, Nie Y, Zhou Y. Fecal microbiota transplantation to treat Parkinson's disease with constipation: A case report. *Medicine (Baltimore)* 2019; **98**: e16163 [PMID: 31261545 DOI: 10.1097/MD.0000000000016163]

15 **Tan AH**, Lim SY, Chong KK, A Manap MAA, Hor JW, Lim JL, Low SC, Chong CW, Mahadeva S, Lang AE. Probiotics for Constipation in Parkinson Disease: A Randomized Placebo-Controlled Study. *Neurology* 2021; **96**: e772-e782 [PMID: 33046607 DOI: 10.1212/WNL.0000000000010998]

16 **Cassani E**, Privitera G, Pezzoli G, Pusani C, Madio C, Iorio L, Barichella M. Use of probiotics for the treatment of constipation in Parkinson's disease patients. *Minerva Gastroenterol Dietol* 2011; **57**: 117-121 [PMID: 21587143]

17 **Lozupone CA**, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. *Nature* 2012; **489**: 220-230 [PMID: 22972295 DOI: 10.1038/nature11550]

18 **Wang Q**, Luo Y, Ray Chaudhuri K, Reynolds R, Tan EK, Pettersson S. The role of gut dysbiosis in Parkinson's disease: mechanistic insights and therapeutic options. *Brain* 2021; **144**: 2571-2593 [PMID: 33856024 DOI: 10.1093/brain/awab156]

19 **Kaur G**, Behl T, Bungau S, Kumar A, Uddin MS, Mehta V, Zengin G, Mathew B, Shah MA, Arora S. Dysregulation of the Gut-Brain Axis, Dysbiosis and Influence of Numerous Factors on Gut Microbiota Associated Parkinson's Disease. *Curr Neuropharmacol* 2021; **19**: 233-247 [PMID: 32504503 DOI: 10.2174/1570159X18666200606233050]

20 **Mayer EA**, Nance K, Chen S. The Gut-Brain Axis. *Annu Rev Med* 2022; **73**: 439-453 [PMID: 34669431 DOI: 10.1146/annurev-med-042320-014032]

21 **Jankovic J**, Tan EK. Parkinson's disease: etiopathogenesis and treatment. *J Neurol Neurosurg Psychiatry* 2020; **91**: 795-808 [PMID: 32576618 DOI: 10.1136/jnnp-2019-322338]

22 **Braak H**, de Vos RA, Bohl J, Del Tredici K. Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett* 2006; **396**: 67-72 [PMID: 16330147 DOI: 10.1016/j.neulet.2005.11.012]

23 **Hawkes CH**, Del Tredici K, Braak H. Parkinson's disease: a dual-hit hypothesis. *Neuropathol Appl Neurobiol* 2007; **33**: 599-614 [PMID: 17961138 DOI: 10.1111/j.1365-2990.2007.00874.x]

24 **Holmqvist S**, Chutna O, Bousset L, Aldrin-Kirk P, Li W, Björklund T, Wang ZY, Roybon L, Melki R, Li JY. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. *Acta Neuropathol* 2014; **128**: 805-820 [PMID: 25296989 DOI: 10.1007/s00401-014-1343-6]

25 **Pan-Montojo F**, Schwarz M, Winkler C, Arnhold M, O'Sullivan GA, Pal A, Said J, Marsico G, Verbavatz JM, Rodrigo-Angulo M, Gille G, Funk RH, Reichmann H. Environmental toxins trigger PD-like progression via increased alpha-synuclein release from enteric neurons in mice. *Sci Rep* 2012; **2**: 898 [PMID: 23205266 DOI: 10.1038/srep00898]

26 **Anselmi L**, Bove C, Coleman FH, Le K, Subramanian MP, Venkiteswaran K, Subramanian T, Travagli RA. Ingestion of subthreshold doses of environmental toxins induces ascending Parkinsonism in the rat. *NPJ Parkinsons Dis* 2018; **4**: 30 [PMID: 30302391 DOI: 10.1038/s41531-018-0066-0]

27 **Kim S**, Kwon SH, Kam TI, Panicker N, Karuppagounder SS, Lee S, Lee JH, Kim WR, Kook M, Foss CA, Shen C, Lee H, Kulkarni S, Pasricha PJ, Lee G, Pomper MG, Dawson VL, Dawson TM, Ko HS. Transneuronal Propagation of Pathologic α-Synuclein from the Gut to the Brain Models Parkinson's Disease. *Neuron* 2019; **103**: 627-641.e7 [PMID: 31255487 DOI: 10.1016/j.neuron.2019.05.035]

28 **Svensson E**, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, Sørensen HT. Vagotomy and subsequent risk of Parkinson's disease. *Ann Neurol* 2015; **78**: 522-529 [PMID: 26031848 DOI: 10.1002/ana.24448]

29 **Shannon KM**, Keshavarzian A, Dodiya HB, Jakate S, Kordower JH. Is alpha-synuclein in the colon a biomarker for premotor Parkinson's disease? Evidence from 3 cases. *Mov Disord* 2012; **27**: 716-719 [PMID: 22550057 DOI: 10.1002/mds.25020]

30 **Hilton D**, Stephens M, Kirk L, Edwards P, Potter R, Zajicek J, Broughton E, Hagan H, Carroll C. Accumulation of α-synuclein in the bowel of patients in the pre-clinical phase of Parkinson's disease. *Acta Neuropathol* 2014; **127**: 235-241 [PMID: 24240814 DOI: 10.1007/s00401-013-1214-6]

31 **Pouclet H**, Lebouvier T, Coron E, des Varannes SB, Rouaud T, Roy M, Neunlist M, Derkinderen P. A comparison between rectal and colonic biopsies to detect Lewy pathology in Parkinson's disease. *Neurobiol Dis* 2012; **45**: 305-309 [PMID: 21878391 DOI: 10.1016/j.nbd.2011.08.014]

32 **Noyce AJ**, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, Schrag A. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann Neurol* 2012; **72**: 893-901 [PMID: 23071076 DOI: 10.1002/ana.23687]

33 **Adams-Carr KL**, Bestwick JP, Shribman S, Lees A, Schrag A, Noyce AJ. Constipation preceding Parkinson's disease: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016; **87**: 710-716 [PMID: 26345189 DOI: 10.1136/jnnp-2015-311680]

34 **Fasano A**, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol* 2015; **14**: 625-639 [PMID: 25987282 DOI: 10.1016/S1474-4422(15)00007-1]

35 **Kaye J**, Gage H, Kimber A, Storey L, Trend P. Excess burden of constipation in Parkinson's disease: a pilot study. *Mov Disord* 2006; **21**: 1270-1273 [PMID: 16700046 DOI: 10.1002/mds.20942]

36 **Scheperjans F**, Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E, Haapaniemi E, Kaakkola S, Eerola-Rautio J, Pohja M, Kinnunen E, Murros K, Auvinen P. Gut microbiota are related to Parkinson's disease and clinical phenotype. *Mov Disord* 2015; **30**: 350-358 [PMID: 25476529 DOI: 10.1002/mds.26069]

37 **Lin CH**, Lin JW, Liu YC, Chang CH, Wu RM. Risk of Parkinson's disease following severe constipation: a nationwide population-based cohort study. *Parkinsonism Relat Disord* 2014; **20**: 1371-1375 [PMID: 25293395 DOI: 10.1016/j.parkreldis.2014.09.026]

38 **Flint HJ**, Duncan SH, Scott KP, Louis P. Interactions and competition within the microbial community of the human colon: links between diet and health. *Environ Microbiol* 2007; **9**: 1101-1111 [PMID: 17472627 DOI: 10.1111/j.1462-2920.2007.01281.x]

39 **Edwards LL**, Quigley EM, Harned RK, Hofman R, Pfeiffer RF. Characterization of swallowing and defecation in Parkinson's disease. *Am J Gastroenterol* 1994; **89**: 15-25 [PMID: 8273792]

40 **Grillo P**, Sancesario GM, Mascioli D, Geusa L, Zenuni H, Giannella E, Della Morte D, Mercuri NB, Schirinzi T. Constipation distinguishes different clinical-biochemical patterns in de novo Parkinson's disease. *Parkinsonism Relat Disord* 2022; **102**: 64-67 [PMID: 35963045 DOI: 10.1016/j.parkreldis.2022.08.001]

41 **Edwards L**, Quigley EM, Hofman R, Pfeiffer RF. Gastrointestinal symptoms in Parkinson disease: 18-month follow-up study. *Mov Disord* 1993; **8**: 83-86 [PMID: 8093549 DOI: 10.1002/mds.870080115]

42 **Chen H**, Zhao EJ, Zhang W, Lu Y, Liu R, Huang X, Ciesielski-Jones AJ, Justice MA, Cousins DS, Peddada S. Meta-analyses on prevalence of selected Parkinson's nonmotor symptoms before and after diagnosis. *Transl Neurodegener* 2015; **4**: 1 [PMID: 25671103 DOI: 10.1186/2047-9158-4-1]

43 **Jones JD**, Rahmani E, Garcia E, Jacobs JP. Gastrointestinal symptoms are predictive of trajectories of cognitive functioning in de novo Parkinson's disease. *Parkinsonism Relat Disord* 2020; **72**: 7-12 [PMID: 32058266 DOI: 10.1016/j.parkreldis.2020.01.009]

44 **Santos García D**, García Roca L, de Deus Fonticoba T, Cores Bartolomé C, Naya Ríos L, Canfield H, Paz González JM, Martínez Miró C, Jesús S, Aguilar M, Pastor P, Planellas L, Cosgaya M, García Caldentey J, Caballol N, Legarda I, Hernández Vara J, Cabo I, López Manzanares L, González Aramburu I, Ávila Rivera MA, Gómez Mayordomo V, Nogueira V, Puente V, Dotor García-Soto J, Borrué C, Solano Vila B, Álvarez Sauco M, Vela L, Escalante S, Cubo E, Carrillo Padilla F, Martínez Castrillo JC, Sánchez Alonso P, Alonso Losada MG, López Ariztegui N, Gastón I, Kulisevsky J, Blázquez Estrada M, Seijo M, Rúiz Martínez J, Valero C, Kurtis M, de Fábregues O, González Ardura J, Alonso Redondo R, Ordás C, López Díaz L LM, McAfee D, Martinez-Martin P, Mir P; COPPADIS Study Group. Constipation Predicts Cognitive Decline in Parkinson's Disease: Results from the COPPADIS Cohort at 2-Year Follow-up and Comparison with a Control Group. *J Parkinsons Dis* 2022; **12**: 315-331 [PMID: 34602501 DOI: 10.3233/JPD-212868]

45 **Camacho M**, Macleod AD, Maple-Grødem J, Evans JR, Breen DP, Cummins G, Wijeyekoon RS, Greenland JC, Alves G, Tysnes OB, Lawson RA, Barker RA, Williams-Gray CH. Early constipation predicts faster dementia onset in Parkinson's disease. *NPJ Parkinsons Dis* 2021; **7**: 45 [PMID: 34039994 DOI: 10.1038/s41531-021-00191-w]

46 **Yong VW**, Tan YJ, Ng YD, Choo XY, Sugumaran K, Chinna K, Md Shah MN, Raja Aman RRA, Moy FM, Mohd Ramli N, Grossmann M, Lim SY, Tan AH. Progressive and accelerated weight and body fat loss in Parkinson's disease: A three-year prospective

longitudinal study. *Parkinsonism Relat Disord* 2020; **77**: 28-35 [PMID: 32615497 DOI: 10.1016/j.parkreldis.2020.06.015]

47 **Kenna JE**, Bakeberg MC, Gorecki AM, Chin Yen Tay A, Winter S, Mastaglia FL, Anderton RS. Characterization of Gastrointestinal Symptom Type and Severity in Parkinson's Disease: A Case-Control Study in an Australian Cohort. *Mov Disord Clin Pract* 2021; **8**: 245-253 [PMID: 33553495 DOI: 10.1002/mdc3.13134]

48 **Khoshbin K**, Hassan A, Camilleri M. Cohort Study in Parkinsonism: Delayed Transit, Accelerated Gastric Emptying, and Prodromal Dysmotility. *Neurol Clin Pract* 2021; **11**: e407-e413 [PMID: 34484938 DOI: 10.1212/CPJ.0000000000001003]

49 **Maini Rekdal V**, Bess EN, Bisanz JE, Turnbaugh PJ, Balskus EP. Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism. *Science* 2019; **364** [PMID: 31196984 DOI: 10.1126/science.aau6323]

50 **van Kessel SP**, Bullock A, van Dijk G, El Aidy S. Parkinson's Disease Medication Alters Small Intestinal Motility and Microbiota Composition in Healthy Rats. *mSystems* 2022; **7**: e0119121 [PMID: 35076270 DOI: 10.1128/msystems.01191-21]

51 **van Kessel SP**, Frye AK, El-Gendy AO, Castejon M, Keshavarzian A, van Dijk G, El Aidy S. Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease. *Nat Commun* 2019; **10**: 310 [PMID: 30659181 DOI: 10.1038/s41467-019-08294-y]

52 **van Kessel SP**, Auvinen P, Scheperjans F, El Aidy S. Gut bacterial tyrosine decarboxylase associates with clinical variables in a longitudinal cohort study of Parkinsons disease. *NPJ Parkinsons Dis* 2021; **7**: 115 [PMID: 34911958 DOI: 10.1038/s41531-021-00260-0]

53 **Kulisevsky J**, Pagonabarraga J. Tolerability and safety of ropinirole versus other dopamine agonists and levodopa in the treatment of Parkinson's disease: meta-analysis of randomized controlled trials. *Drug Saf* 2010; **33**: 147-161 [PMID: 20082541 DOI: 10.2165/11319860-000000000-00000]

54 **Müller B**, Assmus J, Larsen JP, Haugarvoll K, Skeie GO, Tysnes OB; ParkWest study group. Autonomic symptoms and dopaminergic treatment in de novo Parkinson's disease. *Acta Neurol Scand* 2013; **127**: 290-294 [PMID: 22998158 DOI: 10.1111/ane.12010]

55 **Hauser RA**, Schapira AH, Rascol O, Barone P, Mizuno Y, Salin L, Haaksma M, Juhel N, Poewe W. Randomized, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease. *Mov Disord* 2010; **25**: 2542-2549 [PMID: 20669317 DOI: 10.1002/mds.23317]

56 **Pagano G**, Tan EE, Haider JM, Bautista A, Tagliati M. Constipation is reduced by beta-blockers and increased by dopaminergic medications in Parkinson's disease. *Parkinsonism Relat Disord* 2015; **21**: 120-125 [PMID: 25483722 DOI: 10.1016/j.parkreldis.2014.11.015]

57 **Jost WH**, Schimrigk K. Constipation in Parkinson's disease. *Klin Wochenschr* 1991; **69**: 906-909 [PMID: 1795497 DOI: 10.1007/BF01798536]

58 **Knudsen K**, Fedorova TD, Bekker AC, Iversen P, Østergaard K, Krogh K, Borghammer P. Objective Colonic Dysfunction is Far more Prevalent than Subjective Constipation in Parkinson's Disease: A Colon Transit and Volume Study. *J Parkinsons Dis* 2017; **7**: 359-367 [PMID: 28157109 DOI: 10.3233/JPD-161050]

59 **Stirpe P**, Hoffman M, Badiali D, Colosimo C. Constipation: an emerging risk factor for Parkinson's disease? *Eur J Neurol* 2016; **23**: 1606-1613 [PMID: 27444575 DOI: 10.1111/ene.13082]

60 **Cersosimo MG**, Benarroch EE. Pathological correlates of gastrointestinal dysfunction in Parkinson's disease. *Neurobiol Dis* 2012; **46**: 559-564 [PMID: 22048068 DOI: 10.1016/j.nbd.2011.10.014]

61 **Stocchi F**, Torti M. Constipation in Parkinson's Disease. *Int Rev Neurobiol* 2017; **134**: 811-826 [PMID: 28805584 DOI: 10.1016/bs.irn.2017.06.003]

62 **Singaram C**, Ashraf W, Gaumnitz EA, Torbey C, Sengupta A, Pfeiffer R, Quigley EM. Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation. *Lancet* 1995; **346**: 861-864 [PMID: 7564669 DOI: 10.1016/S0140-6736(95)92707-7]

63 **Li ZS**, Schmauss C, Cuenca A, Ratcliffe E, Gershon MD. Physiological modulation of intestinal motility by enteric dopaminergic neurons and the D2 receptor: analysis of dopamine receptor expression, location, development, and function in wild-type and knock-out mice. *J Neurosci* 2006; **26**: 2798-2807 [PMID: 16525059 DOI: 10.1523/JNEUROSCI.4720-05.2006]

64 **Phillips RJ**, Pairitz JC, Powley TL. Age-related neuronal loss in the submucosal plexus of the colon of Fischer 344 rats. *Neurobiol Aging* 2007; **28**: 1124-1137 [PMID: 16793176 DOI: 10.1016/j.neurobiolaging.2006.05.019]

65 **Phillips RJ**, Powley TL. Innervation of the gastrointestinal tract: patterns of aging. *Auton Neurosci* 2007; **136**: 1-19 [PMID: 17537681 DOI: 10.1016/j.autneu.2007.04.005]

66 **Song EM**, Lee HJ, Jung KW, Kim MJ, Hwang SW, Park SH, Yang DH, Ye BD, Byeon JS, Choe J, Yang SK, Rao SSC, Myung SJ. Long-Term Risks of Parkinson's Disease, Surgery, and Colorectal Cancer in Patients With Slow-Transit Constipation. *Clin Gastroenterol Hepatol* 2021; **19**: 2577-2586.e6 [PMID: 32882425 DOI: 10.1016/j.cgh.2020.08.059]

67 **Bassotti G**, Maggio D, Battaglia E, Giulietti O, Spinozzi F, Reboldi G, Serra AM, Emanuelli G, Chiarioni G. Manometric investigation of anorectal function in early and late stage Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2000; **68**: 768-770 [PMID: 10811703 DOI: 10.1136/jnnp.68.6.768]

68 **Mathers SE**, Kempster PA, Swash M, Lees AJ. Constipation and paradoxical puborectalis contraction in anismus and Parkinson's disease: a dystonic phenomenon? *J Neurol Neurosurg Psychiatry* 1988; **51**: 1503-1507 [PMID: 3221217 DOI: 10.1136/jnnp.51.12.1503]

69 **Mathers SE**, Kempster PA, Law PJ, Frankel JP, Bartram CI, Lees AJ, Stern GM, Swash M. Anal sphincter dysfunction in Parkinson's disease. *Arch Neurol* 1989; **46**: 1061-1064 [PMID: 2803065 DOI: 10.1001/archneur.1989.00520460037010]

70 **Edwards LL**, Pfeiffer RF, Quigley EM, Hofman R, Balluff M. Gastrointestinal symptoms in Parkinson's disease. *Mov Disord* 1991; **6**: 151-156 [PMID: 2057006 DOI: 10.1002/mds.870060211]

71 **Gries M**, Christmann A, Schulte S, Weyland M, Rommel S, Martin M, Baller M, Röth R, Schmitteckert S, Unger M, Liu Y, Sommer F, Mühlhaus T, Schroda M, Timmermans JP, Pintelon I, Rappold GA, Britschgi M, Lashuel H, Menger MD, Laschke MW, Niesler B, Schäfer KH. Parkinson mice show functional and molecular changes in the gut long before motoric disease onset. *Mol Neurodegener* 2021; **16**: 34 [PMID: 34078425 DOI: 10.1186/s13024-021-00439-2]

72 **Sampson TR**, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, Challis C, Schretter CE, Rocha S, Gradinaru V, Chesselet MF, Keshavarzian A, Shannon KM, Krajmalnik-Brown R, Wittung-Stafshede P, Knight R, Mazmanian SK. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. *Cell* 2016; **167**: 1469-1480.e12 [PMID: 27912057 DOI: 10.1016/j.cell.2016.11.018]

73 **Matheoud D**, Cannon T, Voisin A, Penttinen AM, Ramet L, Fahmy AM, Ducrot C, Laplante A, Bourque MJ, Zhu L, Cayrol R, Le Campion A, McBride HM, Gruenheid S, Trudeau LE, Desjardins M. Intestinal infection triggers Parkinson's disease-like symptoms in Pink1(-/-) mice. *Nature* 2019; **571**: 565-569 [PMID: 31316206 DOI: 10.1038/s41586-019-1405-y]

74 **Seguella L**, Sarnelli G, Esposito G. Leaky gut, dysbiosis, and enteric glia activation: the trilogy behind the intestinal origin of Parkinson's disease. *Neural Regen Res* 2020; **15**: 1037-1038 [PMID: 31823880 DOI: 10.4103/1673-5374.270308]

75 **Keshavarzian A**, Green SJ, Engen PA, Voigt RM, Naqib A, Forsyth CB, Mutlu E, Shannon KM. Colonic bacterial composition in Parkinson's disease. *Mov Disord* 2015; **30**: 1351-1360 [PMID: 26179554 DOI: 10.1002/mds.26307]

76 **Houser MC**, Tansey MG. The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis? *NPJ Parkinsons Dis* 2017; **3**: 3 [PMID: 28649603 DOI: 10.1038/s41531-016-0002-0]

77 **Kelly LP**, Carvey PM, Keshavarzian A, Shannon KM, Shaikh M, Bakay RA, Kordower JH. Progression of intestinal permeability changes and alpha-synuclein expression in a mouse model of Parkinson's disease. *Mov Disord* 2014; **29**: 999-1009 [PMID: 24898698 DOI: 10.1002/mds.25736]

78 **Ayers JI**, Brooks MM, Rutherford NJ, Howard JK, Sorrentino ZA, Riffe CJ, Giasson BI. Robust Central Nervous System Pathology in Transgenic Mice following Peripheral Injection of α-Synuclein Fibrils. *J Virol* 2017; **91** [PMID: 27852849 DOI: 10.1128/JVI.02095-16]

79 **Luk KC**, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, Lee VM. Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. *Science* 2012; **338**: 949-953 [PMID: 23161999 DOI: 10.1126/science.1227157]

80 **Choi JG**, Kim N, Ju IG, Eo H, Lim SM, Jang SE, Kim DH, Oh MS. Oral administration of Proteus mirabilis damages dopaminergic neurons and motor functions in mice. *Sci Rep* 2018; **8**: 1275 [PMID: 29352191 DOI: 10.1038/s41598-018-19646-x]

81 **Pfeiffer RF**. Gastrointestinal Dysfunction in Parkinson's Disease. *Curr Treat Options Neurol* 2018; **20**: 54 [PMID: 30361783 DOI: 10.1007/s11940-018-0539-9]

82 **Camilleri M**, Subramanian T, Pagan F, Isaacson S, Gil R, Hauser RA, Feldman M, Goldstein M, Kumar R, Truong D, Chhabria N, Walter BL, Eskenazi J, Riesenberg R, Burdick D, Tse W, Molho E, Robottom B, Bhatia P, Kadimi S, Klos K, Shprecher D, Marquez-Mendoza O, Hidalgo G, Grill S, Li G, Mandell H, Hughes M, Stephenson S, Vandersluis J, Pfeffer M, Duker A, Shivkumar V, Kinney W, MacDougall J, Zasloff M, Barbut D. Oral ENT-01 Targets Enteric Neurons to Treat Constipation in Parkinson Disease : A Randomized Controlled Trial. *Ann Intern Med* 2022; **175**: 1666-1674 [PMID: 36343348 DOI: 10.7326/M22-1438]

83 **Wang L**, Magen I, Yuan PQ, Subramaniam SR, Richter F, Chesselet MF, Taché Y. Mice overexpressing wild-type human alpha-synuclein display alterations in colonic myenteric ganglia and defecation. *Neurogastroenterol Motil* 2012; **24**: e425-e436 [PMID: 22779732 DOI: 10.1111/j.1365-2982.2012.01974.x]

84 **Rota L**, Pellegrini C, Benvenuti L, Antonioli L, Fornai M, Blandizzi C, Cattaneo A, Colla E. Constipation, deficit in colon contractions and alpha-synuclein inclusions within the colon precede motor abnormalities and neurodegeneration in the central nervous system in a mouse model of alpha-synucleinopathy. *Transl Neurodegener* 2019; **8**: 5 [PMID: 30774946 DOI: 10.1186/s40035-019-0146-z]

85 **Kuo YM**, Nwankwo EI, Nussbaum RL, Rogers J, Maccecchini ML. Translational inhibition of α-synuclein by Posiphen normalizes distal colon motility in transgenic Parkinson mice. *Am J Neurodegener Dis* 2019; **8**: 1-15 [PMID: 30906671]

86 **O'Donovan SM**, Crowley EK, Brown JR, O'Sullivan O, O'Leary OF, Timmons S, Nolan YM, Clarke DJ, Hyland NP, Joyce SA, Sullivan AM, O'Neill C. Nigral overexpression of α-synuclein in a rat Parkinson's disease model indicates alterations in the enteric nervous system and the gut microbiome. *Neurogastroenterol Motil* 2020; **32**: e13726 [PMID: 31576631 DOI: 10.1111/nmo.13726]

87 **Pellegrini C**, Fornai M, Colucci R, Tirotta E, Blandini F, Levandis G, Cerri S, Segnani C, Ippolito C, Bernardini N, Cseri K, Blandizzi C, Haskó G, Antonioli L. Alteration of colonic excitatory tachykininergic motility and enteric inflammation following dopaminergic nigrostriatal neurodegeneration. *J Neuroinflammation* 2016; **13**: 146 [PMID: 27295950 DOI: 10.1186/s12974-016-0608-5]

88 **Barbara G**, Stanghellini V, Brandi G, Cremon C, Di Nardo G, De Giorgio R, Corinaldesi R. Interactions between commensal bacteria and gut sensorimotor function in health and disease. *Am J Gastroenterol* 2005; **100**: 2560-2568 [PMID: 16279914 DOI: 10.1111/j.1572-0241.2005.00230.x]

89 **Wichmann A**, Allahyar A, Greiner TU, Plovier H, Lundén GÖ, Larsson T, Drucker DJ, Delzenne NM, Cani PD, Bäckhed F. Microbial modulation of energy availability in the colon regulates intestinal transit. *Cell Host Microbe* 2013; **14**: 582-590 [PMID: 24237703 DOI: 10.1016/j.chom.2013.09.012]

90 **Obata Y**, Castaño Á, Boeing S, Bon-Frauches AC, Fung C, Fallesen T, de Agüero MG, Yilmaz B, Lopes R, Huseynova A, Horswell S, Maradana MR, Boesmans W, Vanden Berghe P, Murray AJ, Stockinger B, Macpherson AJ, Pachnis V. Neuronal programming by microbiota regulates intestinal physiology. *Nature* 2020; **578**: 284-289 [PMID: 32025031 DOI: 10.1038/s41586-020-1975-8]

91 **Bhattarai Y**, Si J, Pu M, Ross OA, McLean PJ, Till L, Moor W, Grover M, Kandimalla KK, Margolis KG, Farrugia G, Kashyap PC. Role of gut microbiota in regulating gastrointestinal dysfunction and motor symptoms in a mouse model of Parkinson's

disease. *Gut Microbes* 2021; **13**: 1866974 [PMID: 33459114 DOI: 10.1080/19490976.2020.1866974]

92 **Tan AH**, Lim SY, Lang AE. The microbiome-gut-brain axis in Parkinson disease - from basic research to the clinic. *Nat Rev Neurol* 2022; **18**: 476-495 [PMID: 35750883 DOI: 10.1038/s41582-022-00681-2]

93 **Cirstea MS**, Yu AC, Golz E, Sundvick K, Kliger D, Radisavljevic N, Foulger LH, Mackenzie M, Huan T, Finlay BB, Appel-Cresswell S. Microbiota Composition and Metabolism Are Associated With Gut Function in Parkinson's Disease. *Mov Disord* 2020; **35**: 1208-1217 [PMID: 32357258 DOI: 10.1002/mds.28052]

94 **Barichella M**, Severgnini M, Cilia R, Cassani E, Bolliri C, Caronni S, Ferri V, Cancello R, Ceccarani C, Faierman S, Pinelli G, De Bellis G, Zecca L, Cereda E, Consolandi C, Pezzoli G. Unraveling gut microbiota in Parkinson's disease and atypical parkinsonism. *Mov Disord* 2019; **34**: 396-405 [PMID: 30576008 DOI: 10.1002/mds.27581]

95 **Hill-Burns EM**, Debelius JW, Morton JT, Wissemann WT, Lewis MR, Wallen ZD, Peddada SD, Factor SA, Molho E, Zabetian CP, Knight R, Payami H. Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. *Mov Disord* 2017; **32**: 739-749 [PMID: 28195358 DOI: 10.1002/mds.26942]

96 **Aho VTE**, Pereira PAB, Voutilainen S, Paulin L, Pekkonen E, Auvinen P, Scheperjans F. Gut microbiota in Parkinson's disease: Temporal stability and relations to disease progression. *EBioMedicine* 2019; **44**: 691-707 [PMID: 31221587 DOI: 10.1016/j.ebiom.2019.05.064]

97 **Bedarf JR**, Hildebrand F, Coelho LP, Sunagawa S, Bahram M, Goeser F, Bork P, Wüllner U. Functional implications of microbial and viral gut metagenome changes in early stage L-DOPA-naïve Parkinson's disease patients. *Genome Med* 2017; **9**: 39 [PMID: 28449715 DOI: 10.1186/s13073-017-0428-y]

98 **Cao H**, Liu X, An Y, Zhou G, Liu Y, Xu M, Dong W, Wang S, Yan F, Jiang K, Wang B. Dysbiosis contributes to chronic constipation development via regulation of serotonin transporter in the intestine. *Sci Rep* 2017; **7**: 10322 [PMID: 28871143 DOI: 10.1038/s41598-017-10835-8]

99 **Soret R**, Chevalier J, De Coppet P, Poupeau G, Derkinderen P, Segain JP, Neunlist M. Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats. *Gastroenterology* 2010; **138**: 1772-1782 [PMID: 20152836 DOI: 10.1053/j.gastro.2010.01.053]

100 **Heinzel S**, Aho VTE, Suenkel U, von Thaler AK, Schulte C, Deuschle C, Paulin L, Hantunen S, Brockmann K, Eschweiler GW, Maetzler W, Berg D, Auvinen P, Scheperjans F. Gut Microbiome Signatures of Risk and Prodromal Markers of Parkinson Disease. *Ann Neurol* 2021; **90**: E1-E12 [PMID: 34021620 DOI: 10.1002/ana.26128]

101 **Cakmak YO**. Provotella-derived hydrogen sulfide, constipation, and neuroprotection in Parkinson's disease. *Mov Disord* 2015; **30**: 1151 [PMID: 25970839 DOI: 10.1002/mds.26258]

102 **Martinez-Cutillas M**, Gil V, Mañé N, Clavé P, Gallego D, Martin MT, Jimenez M. Potential role of the gaseous mediator hydrogen sulphide (H2S) in inhibition of human colonic contractility. *Pharmacol Res* 2015; **93**: 52-63 [PMID: 25641403 DOI: 10.1016/j.phrs.2015.01.002]

103 **Chen ZJ**, Liang CY, Yang LQ, Ren SM, Xia YM, Cui L, Li XF, Gao BL. Association of Parkinson's Disease With Microbes and Microbiological Therapy. *Front Cell Infect Microbiol* 2021; **11**: 619354 [PMID: 33763383 DOI: 10.3389/fcimb.2021.619354]

104 **Vandeputte D**, Falony G, Vieira-Silva S, Tito RY, Joossens M, Raes J. Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates. *Gut* 2016; **65**: 57-62 [PMID: 26069274 DOI: 10.1136/gutjnl-2015-309618]

105 **Ceresola ER**, Ferrarese R, Preti A, Canducci F. Targeting patients' microbiota with probiotics and natural fibers in adults and children with constipation. *Eur Rev Med Pharmacol Sci* 2018; **22**: 7045-7057 [PMID: 30402873 DOI: 10.26355/eurrev_201810_16177]

106 **Dao MC**, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E, Verger EO, Kayser BD, Levenez F, Chilloux J, Hoyles L; MICRO-Obes Consortium, Dumas ME, Rizkalla SW, Doré J, Cani PD, Clément K. Akkermansia muciniphila and improved metabolic health

during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* 2016; **65**: 426-436 [PMID: 26100928 DOI: 10.1136/gutjnl-2014-308778]

107 **Hasegawa S**, Goto S, Tsuji H, Okuno T, Asahara T, Nomoto K, Shibata A, Fujisawa Y, Minato T, Okamoto A, Ohno K, Hirayama M. Intestinal Dysbiosis and Lowered Serum Lipopolysaccharide-Binding Protein in Parkinson's Disease. *PLoS One* 2015; **10**: e0142164 [PMID: 26539989 DOI: 10.1371/journal.pone.0142164]

108 **Sampson TR**, Challis C, Jain N, Moiseyenko A, Ladinsky MS, Shastri GG, Thron T, Needham BD, Horvath I, Debelius JW, Janssen S, Knight R, Wittung-Stafshede P, Gradinaru V, Chapman M, Mazmanian SK. A gut bacterial amyloid promotes α-synuclein aggregation and motor impairment in mice. *Elife* 2020; **9** [PMID: 32043464 DOI: 10.7554/eLife.53111]

109 **Unger MM**, Spiegel J, Dillmann KU, Grundmann D, Philippeit H, Bürmann J, Faßbender K, Schwiertz A, Schäfer KH. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. *Parkinsonism Relat Disord* 2016; **32**: 66-72 [PMID: 27591074 DOI: 10.1016/j.parkreldis.2016.08.019]

110 **Muller PA**, Schneeberger M, Matheis F, Wang P, Kerner Z, Ilanges A, Pellegrino K, Del Mármol J, Castro TBR, Furuichi M, Perkins M, Han W, Rao A, Pickard AJ, Cross JR, Honda K, de Araujo I, Mucida D. Microbiota modulate sympathetic neurons via a gut-brain circuit. *Nature* 2020; **583**: 441-446 [PMID: 32641826 DOI: 10.1038/s41586-020-2474-7]

111 **Martin-Gallausiaux C**, Marinelli L, Blottière HM, Larraufie P, Lapaque N. SCFA: mechanisms and functional importance in the gut. *Proc Nutr Soc* 2021; **80**: 37-49 [PMID: 32238208 DOI: 10.1017/S0029665120006916]

112 **Yajima T**. Contractile effect of short-chain fatty acids on the isolated colon of the rat. *J Physiol* 1985; **368**: 667-678 [PMID: 2867220 DOI: 10.1113/jphysiol.1985.sp015882]

113 **Cherbut C**, Ferrier L, Rozé C, Anini Y, Blottière H, Lecannu G, Galmiche JP. Short-chain fatty acids modify colonic motility through nerves and polypeptide YY release in the rat. *Am J Physiol* 1998; **275**: G1415-G1422 [PMID: 9843779 DOI: 10.1152/ajpgi.1998.275.6.G1415]

114 **Zhang X**, Li Y, Liu C, Fan R, Wang P, Zheng L, Hong F, Feng X, Zhang Y, Li L, Zhu J. Alteration of enteric monoamines with monoamine receptors and colonic dysmotility in 6-hydroxydopamine-induced Parkinson's disease rats. *Transl Res* 2015; **166**: 152-162 [PMID: 25766133 DOI: 10.1016/j.trsl.2015.02.003]

115 **Wu MJ**, Shin DH, Kim MY, Park CG, Kim YD, Lee J, Park IK, Choi S, So I, Park JS, Jun JY. Functional effects of β3-adrenoceptor on pacemaker activity in interstitial cells of Cajal from the mouse colon. *Eur J Pharmacol* 2015; **754**: 32-40 [PMID: 25725113 DOI: 10.1016/j.ejphar.2015.02.031]

116 **Zizzo MG**, Mulè F, Mastropaolo M, Serio R. D1 receptors play a major role in the dopamine modulation of mouse ileum contractility. *Pharmacol Res* 2010; **61**: 371-378 [PMID: 20138148 DOI: 10.1016/j.phrs.2010.01.015]

117 **Zhang X**, Guo H, Xu J, Li Y, Li L, Zhang X, Li X, Fan R, Zhang Y, Duan Z, Zhu J. Dopamine receptor D1 mediates the inhibition of dopamine on the distal colonic motility. *Transl Res* 2012; **159**: 407-414 [PMID: 22500514 DOI: 10.1016/j.trsl.2012.01.002]

118 **Hoffman JM**, Tyler K, MacEachern SJ, Balemba OB, Johnson AC, Brooks EM, Zhao H, Swain GM, Moses PL, Galligan JJ, Sharkey KA, Greenwood-Van Meerveld B, Mawe GM. Activation of colonic mucosal 5-HT(4) receptors accelerates propulsive motility and inhibits visceral hypersensitivity. *Gastroenterology* 2012; **142**: 844-854.e4 [PMID: 22226658 DOI: 10.1053/j.gastro.2011.12.041]

119 **Morita H**, Mochiki E, Takahashi N, Kawamura K, Watanabe A, Sutou T, Ogawa A, Yanai M, Ogata K, Fujii T, Ohno T, Tsutsumi S, Asao T, Kuwano H. Effects of 5-HT2B, 5-HT3 and 5-HT4 receptor antagonists on gastrointestinal motor activity in dogs. *World J Gastroenterol* 2013; **19**: 6604-6612 [PMID: 24151388 DOI: 10.3748/wjg.v19.i39.6604]

120 **Grider JR**, Piland BE. The peristaltic reflex induced by short-chain fatty acids is mediated by sequential release of 5-HT and neuronal CGRP but not BDNF. *Am J Physiol Gastrointest Liver Physiol* 2007; **292**: G429-G437 [PMID: 16973914 DOI: 10.1152/ajpgi.00376.2006]

121 **Vincent AD**, Wang XY, Parsons SP, Khan WI, Huizinga JD. Abnormal absorptive colonic motor activity in germ-free mice is rectified by butyrate, an effect possibly

mediated by mucosal serotonin. *Am J Physiol Gastrointest Liver Physiol* 2018; **315**: G896-G907 [PMID: 30095295 DOI: 10.1152/ajpgi.00237.2017]

122 **Fukumoto S**, Tatewaki M, Yamada T, Fujimiya M, Mantyh C, Voss M, Eubanks S, Harris M, Pappas TN, Takahashi T. Short-chain fatty acids stimulate colonic transit via intraluminal 5-HT release in rats. *Am J Physiol Regul Integr Comp Physiol* 2003; **284**: R1269-R1276 [PMID: 12676748 DOI: 10.1152/ajpregu.00442.2002]

123 **Tan AH**, Chong CW, Lim SY, Yap IKS, Teh CSJ, Loke MF, Song SL, Tan JY, Ang BH, Tan YQ, Kho MT, Bowman J, Mahadeva S, Yong HS, Lang AE. Gut Microbial Ecosystem in Parkinson Disease: New Clinicobiological Insights from Multi-Omics. *Ann Neurol* 2021; **89**: 546-559 [PMID: 33274480 DOI: 10.1002/ana.25982]

124 **Gaudier E**, Jarry A, Blottière HM, de Coppet P, Buisine MP, Aubert JP, Laboisse C, Cherbut C, Hoebler C. Butyrate specifically modulates MUC gene expression in intestinal epithelial goblet cells deprived of glucose. *Am J Physiol Gastrointest Liver Physiol* 2004; **287**: G1168-G1174 [PMID: 15308471 DOI: 10.1152/ajpgi.00219.2004]

125 **Matsuo K**, Ota H, Akamatsu T, Sugiyama A, Katsuyama T. Histochemistry of the surface mucous gel layer of the human colon. *Gut* 1997; **40**: 782-789 [PMID: 9245933 DOI: 10.1136/gut.40.6.782]

126 **Aho VTE**, Houser MC, Pereira PAB, Chang J, Rudi K, Paulin L, Hertzberg V, Auvinen P, Tansey MG, Scheperjans F. Relationships of gut microbiota, short-chain fatty acids, inflammation, and the gut barrier in Parkinson's disease. *Mol Neurodegener* 2021; **16**: 6 [PMID: 33557896 DOI: 10.1186/s13024-021-00427-6]

127 **Willkommen D**, Lucio M, Moritz F, Forcisi S, Kanawati B, Smirnov KS, Schroeter M, Sigaroudi A, Schmitt-Kopplin P, Michalke B. Metabolomic investigations in cerebrospinal fluid of Parkinson's disease. *PLoS One* 2018; **13**: e0208752 [PMID: 30532185 DOI: 10.1371/journal.pone.0208752]

128 **Baldini F**, Hertel J, Sandt E, Thinnes CC, Neuberger-Castillo L, Pavelka L, Betsou F, Krüger R, Thiele I; NCER-PD Consortium. Parkinson's disease-associated alterations of the gut microbiome predict disease-relevant changes in metabolic functions. *BMC Biol* 2020; **18**: 62 [PMID: 32517799 DOI: 10.1186/s12915-020-00775-7]

129 **Kuai XY**, Yao XH, Xu LJ, Zhou YQ, Zhang LP, Liu Y, Pei SF, Zhou CL. Evaluation of fecal microbiota transplantation in Parkinson's disease patients with constipation. *Microb Cell Fact* 2021; **20**: 98 [PMID: 33985520 DOI: 10.1186/s12934-021-01589-0]

130 **Khalif IL**, Quigley EM, Konovitch EA, Maximova ID. Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. *Dig Liver Dis* 2005; **37**: 838-849 [PMID: 16169298 DOI: 10.1016/j.dld.2005.06.008]

131 **Kim SE**, Choi SC, Park KS, Park MI, Shin JE, Lee TH, Jung KW, Koo HS, Myung SJ; Constipation Research group of Korean Society of Neurogastroenterology and Motility. Change of Fecal Flora and Effectiveness of the Short-term VSL#3 Probiotic Treatment in Patients With Functional Constipation. *J Neurogastroenterol Motil* 2015; **21**: 111-120 [PMID: 25537674 DOI: 10.5056/jnm14048]

132 **Chassard C**, Dapoigny M, Scott KP, Crouzet L, Del'homme C, Marquet P, Martin JC, Pickering G, Ardid D, Eschalier A, Dubray C, Flint HJ, Bernalier-Donadille A. Functional dysbiosis within the gut microbiota of patients with constipated-irritable bowel syndrome. *Aliment Pharmacol Ther* 2012; **35**: 828-838 [PMID: 22315951 DOI: 10.1111/j.1365-2036.2012.05007.x]

133 **Ohkusa T**, Koido S, Nishikawa Y, Sato N. Gut Microbiota and Chronic Constipation: A Review and Update. *Front Med (Lausanne)* 2019; **6**: 19 [PMID: 30809523 DOI: 10.3389/fmed.2019.00019]

134 **Poirier AA**, Aubé B, Côté M, Morin N, Di Paolo T, Soulet D. Gastrointestinal Dysfunctions in Parkinson's Disease: Symptoms and Treatments. *Parkinsons Dis* 2016; **2016**: 6762528 [PMID: 28050310 DOI: 10.1155/2016/6762528]

135 **Barboza JL**, Okun MS, Moshiree B. The treatment of gastroparesis, constipation and small intestinal bacterial overgrowth syndrome in patients with Parkinson's disease. *Expert Opin Pharmacother* 2015; **16**: 2449-2464 [PMID: 26374094 DOI: 10.1517/14656566.2015.1086747]

136 **Gibson GR**, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, Verbeke K, Reid G. Expert consensus document: The

International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 491-502 [PMID: 28611480 DOI: 10.1038/nrgastro.2017.75]

137 **Meksawan K**, Chaotrakul C, Leeaphorn N, Gonlchanvit S, Eiam-Ong S, Kanjanabuch T. Effects of Fructo-Oligosaccharide Supplementation on Constipation in Elderly Continuous Ambulatory Peritoneal Dialysis Patients. *Perit Dial Int* 2016; **36**: 60-66 [PMID: 25292404 DOI: 10.3747/pdi.2014.00015]

138 **Astarloa R**, Mena MA, Sánchez V, de la Vega L, de Yébenes JG. Clinical and pharmacokinetic effects of a diet rich in insoluble fiber on Parkinson disease. *Clin Neuropharmacol* 1992; **15**: 375-380 [PMID: 1330307 DOI: 10.1097/00002826-199210000-00004]

139 **Ashraf W**, Pfeiffer RF, Park F, Lof J, Quigley EM. Constipation in Parkinson's disease: objective assessment and response to psyllium. *Mov Disord* 1997; **12**: 946-951 [PMID: 9399219 DOI: 10.1002/mds.870120617]

140 **Hill C**, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC, Sanders ME. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 506-514 [PMID: 24912386 DOI: 10.1038/nrgastro.2014.66]

141 **Yin S**, Zhu F. Probiotics for constipation in Parkinson's: A systematic review and meta-analysis of randomized controlled trials. *Front Cell Infect Microbiol* 2022; **12**: 1038928 [PMID: 36439217 DOI: 10.3389/fcimb.2022.1038928]

142 **Yan T**, Shi J, Li X. Clinical efficacy of probiotics in the treatment of constipation in Parkinson's patients. *Minerva Gastroenterol (Torino)* 2022; **68**: 369-371 [PMID: 35112821 DOI: 10.23736/S2724-5985.21.03078-3]

143 **Barichella M**, Pacchetti C, Bolliri C, Cassani E, Iorio L, Pusani C, Pinelli G, Privitera G, Cesari I, Faierman SA, Caccialanza R, Pezzoli G, Cereda E. Probiotics and prebiotic fiber for constipation associated with Parkinson disease: An RCT. *Neurology* 2016; **87**: 1274-1280 [PMID: 27543643 DOI: 10.1212/WNL.0000000000003127]

144 **Ibrahim A**, Ali RAR, Manaf MRA, Ahmad N, Tajurruddin FW, Qin WZ, Desa SHM, Ibrahim NM. Multi-strain probiotics (Hexbio) containing MCP BCMC strains improved constipation and gut motility in Parkinson's disease: A randomised controlled trial. *PLoS One* 2020; **15**: e0244680 [PMID: 33382780 DOI: 10.1371/journal.pone.0244680]

145 **Ge X**, Zhao W, Ding C, Tian H, Xu L, Wang H, Ni L, Jiang J, Gong J, Zhu W, Zhu M, Li N. Potential role of fecal microbiota from patients with slow transit constipation in the regulation of gastrointestinal motility. *Sci Rep* 2017; **7**: 441 [PMID: 28348415 DOI: 10.1038/s41598-017-00612-y]

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